AWARD NUMBER: W81XWH-15-1-0605

TITLE: Prevention of Posttraumatic Contractures with Ketotifen (PERK)

PRINCIPAL INVESTIGATOR: Kevin Hildebrand

CONTRACTING ORGANIZATION: Governors of the University of Calgary
Calgary, T2N 1N4
Canada

REPORT DATE: October 2017

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

# REPORT DOCUMENTATION PAGE

*Form Approved*
*OMB No. 0704-0188*



| 1. REPORT DATE *(DD-MM-YYYY)* | 2. REPORT TYPE | 3. DATES COVERED *(From - To)* |
|---|---|---|
| October 2017 | Annual | 30 Sep 2016 - 29 Sep 2017 |

**4. TITLE AND SUBTITLE**

Prevention of Posttraumatic Contractures with Ketotifen (PERK)

**5a. CONTRACT NUMBER**

**5b. GRANT NUMBER**

W81XWH-15-1-0605

**5c. PROGRAM ELEMENT NUMBER**

**6. AUTHOR(S)**

Kevin A. Hildebrand

E-Mail:hildebrk@ucalgary.ca

**5d. PROJECT NUMBER**

**5e. TASK NUMBER**

**5f. WORK UNIT NUMBER**

**7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)**

Governors of the University of Calgary,
2500 University Drive NW
Calgary, AB CANADA T2N 1N4

**8. PERFORMING ORGANIZATION REPORT NUMBER**

**9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)**

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

**10. SPONSOR/MONITOR'S ACRONYM(S)**

**11. SPONSOR/MONITOR'S REPORT NUMBER(S)**

**12. DISTRIBUTION/AVAILABILITY STATEMENT**

Approved for Public Release; Distribution Unlimited

**13. SUPPLEMENTARY NOTES**

**14. ABSTRACT**

A 1-year no cost extension was obtained for this contract. Funding has been secured from PRORP (grant number OR160026) for a Phase III RCT (contract number W81XWH-17-01-0665). An IND application to the FDA has been classified as "clinical hold". We have executed a contract with EXOVA to perform an analysis of ketotifen for trace heavy elements, the outstanding issue leading to the "clinical hold" classification. IRB approval has been obtained at the lead institution for the Phase III RCT. Fifteen other sites have confirmed their participation and will attend 1 of 2 training

**15. SUBJECT TERMS**

Post-traumatic contractures, Randomized Clinical Trial, Elbow fractures, Multicentre, Ketotifen, Placebo controlled, double-blind, data base

| 16. SECURITY CLASSIFICATION OF: | | | 17. LIMITATION OF ABSTRACT | 18. NUMBER OF PAGES | 19a. NAME OF RESPONSIBLE PERSON |
|---|---|---|---|---|---|
| a. REPORT | b. ABSTRACT | c. THIS PAGE | | | USAMRMC |
| U | U | U | UU | 36 | 19b. TELEPHONE NUMBER *(Include area code)* |

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## 1. INTRODUCTION

This Clinical Trial Development Award (CTDA) pertains to the FY14 Peer Reviewed Orthopaedic Research Program (PRORP) Clinical Trial Development Award (CTDA) announcement to identify and reduce secondary health effects (e.g., joint contracture) that follow reduced mobility from traumatic neuromusculoskeletal injury. This CTDA facilitates an opportunity to design a Phase III RCT on the use of ketotifen in post-traumatic joint contractures. The goal is to design and develop the infrastructure to complete a multicenter Phase III RCT. This will facilitate applications for operational funds to complete the Phase III RCT. The identified funding mechanisms are PRORP or Peer Reviewed Medical Research Program (PRMRP) Clinical Trial Award (CTA) competitions and the Canadian Institutes of Health Research (CIHR) for the Phase III RCT.

## 2. KEYWORDS

Post-traumatic contractures, elbow fractures, randomized clinical trial, multicenter, ketotifen, placebo, IND application, data base, training, contracts, institutional review board.

## 3. ACCOMPLISHMENTS

**What were the major goals of the project?**

| Development of Phase III RCT | Timeline | Status |
|---|---|---|
| **Major Task 1 Recruit Sites** | Months | |
| Present at American Society for Surgery of the Hand September 2015 in Seattle | 0 | Completed |
| Present at Canadian Orthopaedic Trauma Society Meeting at the annual Orthopaedic Trauma Association meeting October 2015 San Diego | 1 | Completed |
| Present at Major Extremity Trauma Research Consortium Fall 2015 – Winter 2016. | 4-6 | Cancelled |
| Contact US Military Organizations | 1-6 | Completed |
| Site Investigator and Site Research Coordinator training | 24-27 | In Progress – 30% complete |
| IRB and contract completion | 21-25 | In Progress – 98% complete |
| USAMRMC HRPO review and approval | 24-30 | In Progress – 15% complete |
| **Major Task 2 Regulatory Applications** | Months | |
| Pre-IND Consultation | 1-3 | completed |
| IND Application Completion | 4-6 | completed |
| FDA review, Response to clarification requests or questions | 7-9 | In Progress – 85% complete |
| **Major Task 3 Medication Packaging and Distribution** | Months | |
| Identify Manufacturer Canada and US | 1-3 | Completed |

| | | |
|---|---|---|
| Identify Distributor Canada and US | 1-3 | Completed |
| Finalize manufacture and distribution plan with research design / Clinical Research Unit | 21-30 | In Progress – 50% complete |
| **Major Task 4 Data management and Safety** | Months | |
| Identify database and partner – Clinical Research Unit | 1-2 | Completed |
| Develop Case Report Forms, consent forms | 6-12 | Completed |
| Develop database and multicenter submission process | 22-27 | In progress, 50% completed |
| Develop Xray acquisition and Archiving system | 24-27 | In Progress, 80% complete |
| License for patient reported outcome measures | 15-18 | In Progress – 80% complete |
| Data monitoring / Quality Assurance plan | 22-28 | In Progress – 20% complete |
| DSMB establishment | 26-28 | Pending |
| **Major Task 5 Phase III RCT design** | | |
| Study design, Sample size calculation, Statistical analysis plan | 6-18 | Completed |
| Confounding variable analysis | 12 | Completed |
| **Major Task 6 Transition Plan** | | |
| Phase III RCT design – sample size calculation, statistical analysis plan, outcome measure and confounding variable analysis | 6-18 | Completed |
| Phase III RCT Grant writing – PRORP or PRMRP CTA; CIHR | 6-18 | Completed |
| Public Communication – AHS communication, local media Calgary | 22-30 | In Progress – 20% complete |

**What was accomplished under these goals?**

The major activities achieved include a no cost 1-year extension for this award; confirming participating sites for the multicenter randomized clinical trial (RCT); receiving an award from the PRORP opportunity for a Phase III RCT (OR160026); negotiating a contract for the award (W81XWH-17-01-0665); receiving IRB approval for the RCT from the University of Calgary Conjoint Health Research Ethics Board; submitting an IND application to the FDA; FDA review of the IND application and issuing a "clinical hold" notice; engagement of the manufacturing company for the medication (TEVA Canada); development of a data management and study management plan; and further development of the medication acquisition, packaging and distribution solution for ketotifen and placebo.

A total of 16 sites across North America have been confirmed – 13 in Canada and 3 in the US (Major Task 1). Two of the US sites are part of the Major Extremity Trauma Research Consortium (METRC). The METRC sites are hospitals that manage civilian and military populations. The 16 sites provide access to sufficient numbers of patients to complete the multicenter RCT trial design. These sites were identified through the presentations at the American Society for Surgery of the Hand (ASSH), the Canadian

Orthopaedic Trauma Society (COTS), and contacting US military organizations, and a formal presentation to METRC was not required.

An Operational grant has been secured from the PRORP opportunity (Major Task 6). The Bay Area Research Logistics (BARL) of Hamilton, Ontario was engaged to manufacture and distribute the medications and will interact with TEVA Canada, the supplier of the medication and placebo (Major Task 3). The Clinical Research Unit (CRU) at the Cumming School of Medicine at the University of Calgary has moved forward with the data management and logistical support for conducting the trial (randomization, coordinating distribution with BARL). The Calgary Image Processing and Analysis Centre (CIPAC) will provide image archiving and interpretation for the multicenter RCT. Further work is required on the data base development, imaging acquisition, and consent forms. These are all part of Major Task 4. Writing the operating grants facilitated the design of the Phase III multicenter RCT (Major Task 5). Ketotifen is an oral anti-asthmatic medication and a topic ophthalmic agent for the treatment of allergic conjunctivitis. An FDA IND application to use ketotifen in post-traumatic joint contracture prevention was submitted to the Division of Pulmonary, Allergy, and Rheumatology products at the FDA late July 2017 (Major Task 2). A full clinical hold notice was issued August 30, 2017, and we have contracted EXOVA Group Limited (Santa Fe Springs, CA) to perform a trace analysis for heavy metals to answer the clinical hold notice for the IND application

**What opportunities for training and professional development has the project provided?**

Nothing to Report.

**How were the results disseminated to communities of interest?**

The major reporting activities were the presentations at the ASSH and COTS meetings. The goal was to invite participation in the future Phase III multicenter RCT and to provide input into the design of the RCT. We attended the 2017 meetings in September and October for these 2 organizations.

**What do we plan to do during the next reporting period to accomplish the goals?**

Two investigator meetings to train the site PI and Research coordinator are Scheduled in Calgary the first weekend November 2017 and the first weekend of December 2017. The EXOVA report is expected in early November and then a response will be submitted to the FDA to remove the full clinical hold on the IND application. Final signatures for the full award with the University of Calgary is expected in October 2017. Subaward contracts will then be negotiated with the 15 other sites. Local site IRB will be obtained for the other 15 sites October – December 2017. Further meetings with the CRU to complete the data management and study management components will take place October 2017 – January 2018. Completion of the license application for the Oxford elbow score, the interaction of the image analysis process (CIPAC) with the database / study management through the CRU, and establishment of the data monitoring process and board will be completed by January 2018. An USAMRMC HRPO application will be submitted January 2018. The acquisition, manufacturing, and distribution of the

medication and placebo will begin February 2018. A protocol paper will be submitted for publication in February 2018. The plan is to randomize the first participant in April 2018.

**4. IMPACT**

**What was the impact on the development of the principal discipline(s) of the report?**

Nothing to report.

**What was the impact on other disciplines?**

Nothing to report.

**What was the impact on technology transfer?**

Nothing to report.

**What was the impact on society beyond science and technology?**

Nothing to report.

**5. CHANGES/PROBLEMS**

**Changes in approach and reasons for change**

A no cost 1-year extension was obtained as operational funding for the Phase III RCT had not been secured by March 29, 2017.

**Actual or anticipated problems or delays and actions or plans to resolve them**

No anticipated problems or delays expected.

**Changes that had a significant impact on expenditures**

Expenditures are much lower than anticipated. This relates to the delay in the plans for site personnel training and the application to the IRBs.

**Significant changes in the use or care of human subjects, vertebrate animals, biohazards, and / or select agents**

Not applicable. None of these considerations are relevant to the CTDA.

**6. PRODUCTS**

**Publications, conference papers, presentations**

Nothing to report.

**Website(s) or Internet site(s)**

Nothing to report.

**Technologies or techniques**

Nothing to report.

**Inventions, patent applications, and / or licenses**

Nothing to report.

**Other Products**

Nothing to report.

## 7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

**What individuals have worked on the project?**

| | |
|---|---|
| Name: | Kevin Hildebrand |
| Project Role: | Principal Investigator |
| Research Identifier: | orcid.org/0000-0001-8786-9021 |
| Nearest Person Month worked: | 2 |
| Contribution to Project: | Overall management. Writing grants, study design. Recruiting sites. Obtaining data management, medication partners. |
| Funding Support: | Department of Surgery University of Calgary |

| | |
|---|---|
| Name: | Alex Garven |
| Project Role: | Research Coordinator |
| Research Identifier: | None |
| Nearest Person Month worked: | 3 |
| Contribution to Project: | Regulatory application (IND). Database development. Case report forms, consent. Assist in study design and writing grants. |
| Funding Support: | Partial support from Worker's Compensation Board of Alberta, Division of Orthopaedic Surgery, University of Calgary. |

**Has there been a change in the active support of the PD/PI(s) or senior / key personnel since the last reporting period?**

The successful grant application to the PRORP CTA opportunity (OR160026) that has led to a contract to support a Phase III RCT (W81XWH-17-01-0665) for Kevin A. Hildebrand, MD.

**What other organizations were involved as partners?**

Nothing to report.

## 8. SPECIAL REPORTING REQUIREMENTS

**COLLABORATIVE AWARDS**

Nothing to report.

**QUAD CHARTS**

Year 2 Quarter 4 quad chart is included in the appendices.

## 9. APPENDICES

A. Quad Chart
B. PRORP Funding Notification letter
C. Contract
D. IND Full Clinical Hold notification

E. EXOVA contract
F. University of Calgary Conjoint Health Research Ethics Board approval

# Prevention of Posttraumatic Contractures with Ketotifen (PERK)

OR140142
W81XWH-15-1-0605

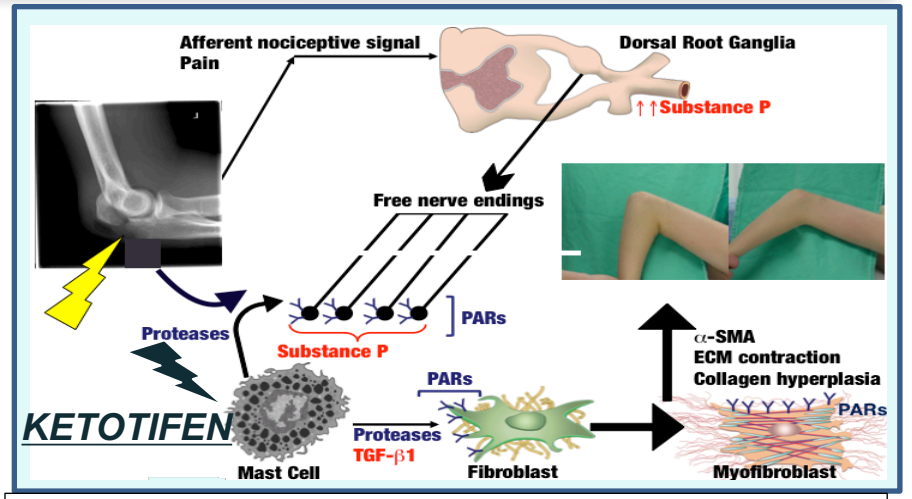
**PI:** Kevin A. Hildebrand **Org:** University of Calgary **Award Amount:** $238,420

## Study/Product Aim(s)

- Major Task 1 – Recruit sites
- Major Task 2 – Regulatory applications
- Major Task 3 – Medication Packaging & Distribution
- Major Task 4 – Data Management and Safety
- Major Task 5 – Phase III RCT design
- Major Task 6 – Transition Plan

## Approach

This is a clinical trial development award. The goal is to design and develop the infrastructure to complete a multicenter Phase III RCT. Regulatory; Ethics; data base and study management; medication acquisition, double blind production, and distribution; identification and training of sites personnel; and applications to PRORP or PRMRP Clinical Trial Award competitions and to the Canadian Institutes of Health Research (CIHR) for operational funds will occur.




IND application clinical hold. Working on answers to clinical hold. IRB approval for lead site for Calgary sites. PRORP application was successful and contract awarded for Phase III multicenter RCT. Site confirmation and training study personnel scheduled.

## Timeline and Cost

| Activities CY | 15 | 16 | 17 | 18 |
|---|---|---|---|---|
| PRORP-CTA Contract | | | | |
| HRPO application | | | | |
| IND application | | | | |
| IRB application | | | | |
| **Estimated Budget ($K)** | **$19** | **$208** | **$11** | **$000** |

**Updated:** (September 29, 2017)

**Goals/Milestones**

**CY16/17 Goal** – PRORP-CTA

☑ Contract W81XWH-17-01-0665 was awarded for funding September 30, 2017

**CY17 Goals** – HRPO application

☑ Started

☐ Submitted

**CY16/17 Goal** – IND

☑Clinical Hold status August 30, 2017

☐ EXOVA performing heavy element analysis addressing clinical hold

**CY17 IRB application**– Site Recruitment

☑ Calgary – Peter Lougheed Centre approved 11 Sep 2017

☐ Other 15 sites

**Comments/Challenges/Issues/Concerns**

- Training site personnel, database and study management next steps. Goal is to randomize first participant April 2018.

**Budget Expenditure to Date**

Projected Expenditure:$238,420 Actual Expenditure: $45,914

**DEPARTMENT OF THE ARMY**
US ARMY MEDICAL RESEARCH ACQUISITION ACTIVITY
820 CHANDLER STREET
FORT DETRICK MD 21702-5014

REPLY TO
ATTENTION OF

May 30, 2017

Assistance Agreements Group

Kevin Hildebrand
University of Calgary
Department of Surgery
2500 University Drive NW

Calgary, AB T2N 1N4
CANADA
hildebrk@ucalgary.ca

RE: OR160026 - "Prevention of Post-Traumatic Contractures with Ketotifen II (PERK II)"

STATUS: RECOMMENDED FOR FUNDING

Dear Kevin Hildebrand:

Congratulations! On behalf of the Department of Defense office of the Congressionally Directed Medical Research Programs (CDMRP), I am pleased to inform you that the Fiscal Year 2016 Peer Reviewed Orthopaedic Research Program (PRORP) Clinical Trial Award application you submitted was recommended for funding. Funding recommendations were made at a second-tier, programmatic review meeting based on program goals and scientific merit. The peer review summary statement for this application and an information paper highlighting the two-tier review process are posted under your electronic Biomedical Research Application Portal (eBRAP) (https://ebrap.org/eBRAP/public/Program.htm) account.

Additional documentation is needed to start the award process. Your timely submission of all applicable documents in the appropriate formats will expedite this process and the release of funds. A CDMRP Science Officer will be your scientific and technical point of contact throughout the life of this award and may contact you for further information regarding various aspects of your application. For example, your Science Officer may contact you about animal use and human use documents that may be needed for your project. Together, you will set a target date for the submission of your complete animal use or human use appendix documents. The Surety and Environmental Office will contact you if any Environmental Compliance Assurance documents are necessary.

A Grants/Contract Specialist from the US Army Medical Research Acquisition Activity (USAMRAA) will contact the Business Official (person authorized to conduct negotiations) at your institution to begin award negotiations. All official negotiations of the budget, terms, and conditions of any resulting award will be limited to the Business Official of your institution and the USAMRAA Grants/Contract Specialist.

Your performance on any previous US Army Medical Research and Materiel Command sponsored awards will be considered during negotiations. As such, you are advised to review your current and past awards to ensure that all required information has been submitted, including all technical reporting and regulatory oversight documents and all financial reports, as this may impact the negotiation and award process.

If you are withdrawing your application, please co-sign a letter of withdrawal with a Business Official at your institution and upload it under the "Required Award Information" tab on eBRAP (https://eBRAP.org).

To expedite the award process, please answer the post-submission questions found under the "Required Award Information" tab on eBRAP by June 6, 2017. For additional information, consult the "Guide for Funded Investigators," which can be found in the "Resources and Reference Material" section under the "Funding Opportunities and Forms" tab on eBRAP. Please especially note the following when supplying the information requested under the above-mentioned tab:

- You and your institution are responsible for ensuring that there is no duplication of the science, budget, or level of effort in separately funded studies in which you were or currently are involved. If you received funding for any portion of this application from another source, or if any portion of the proposed work has already started, please indicate so under this tab.

- Updated details on all support for the past 5 years, existing support, and pending support for yourself and key personnel, including the title of the project, goals, specific aims/tasks, estimated start date and end date, level of effort (percentage or calendar months) in the project, and point of contact at the funding agency. Provide a cover letter signed by a Business Official, certifying that this information is current and accurate, and addresses any scientific or financial overlap.

A copy of this notification is being made available to your institution's Business Official.

Again, congratulations on the recommendation of your application for funding. The CDMRP staff and I look forward to working with you to realize the vision of the PRORP. Please direct any questions to the CDMRP Help Desk at help@eBRAP.org or 301-682-5507.

Please note that awards are subject to negotiations and availability of funds.

Sincerely,

Teresa M. Parker Reeser
Grants Officer

Cc: Akua N. Roach, Ph.D.
PRORP, Program Manager

# AWARD/CONTRACT

| 1. THIS CONTRACT IS A RATED ORDER UNDER DPAS (15 CFR 700) | RATING | PAGE OF PAGES |
|---|---|---|
| | | 1 \| 17 |

| 2. CONTRACT (Proc. Inst. Ident.) NO. | 3. EFFECTIVE DATE | 4. REQUISITION/PURCHASE REQUEST/PROJECT NO. |
|---|---|---|
| W81XWH-17-1-0665 | 30 Sep 2017 | 0011096131 |

| 5. ISSUED BY | CODE | 6. ADMINISTERED BY (If other than Item 5) | CODE |
|---|---|---|---|
| USA MED RESEARCH ACQ ACTIVITY<br>820 CHANDLER ST<br>FORT DETRICK MD 21702-5014 | W81XWH | **See Item 5** | |

| 7. NAME AND ADDRESS OF CONTRACTOR (No., street, city, county, state and zip code) | 8. DELIVERY | ITEM |
|---|---|---|
| GOVERNORS OF THE UNIVERSITY OF CALGARY,<br>2500 UNIVERSITY DR NW<br>CALGARY T2N 1N4 | [ ] FOB ORIGIN [ X ] OTHER (See below) | |
| | 9. DISCOUNT FOR PROMPT PAYMENT<br>Net 30 Days | |
| | 10. SUBMIT INVOICES 1 (4 copies unless otherwise specified) TO THE ADDRESS SHOWN IN: | |
| CODE 1C344 | FACILITY CODE | |

| 11. SHIP TO/MARK FOR | CODE | 12. PAYMENT WILL BE MADE BY | CODE |
|---|---|---|---|
| FORT DETRICK - CDMRP<br>FORT DETRICK - CDMRP<br>1120 FORT DETRICK<br>FREDERICK MD 21702 | W91ZSQ | DEFENSE FINANCE AND ACCOUNTING SERVICE<br>DFAS-INDY VP GFEBS<br>8899 E 56TH STREET<br>INDIANAPOLIS IN 46249-3800 | HQ0490 |

| 13. AUTHORITY FOR USING OTHER THAN FULL AND OPEN COMPETITION:<br>[ ] 10 U.S.C. 2304(c)( ) [ ] 41 U.S.C. 253(c)( ) | 14. ACCOUNTING AND APPROPRIATION DATA<br>**See Schedule** |
|---|---|

| 15A. ITEM NO. | 15B. SUPPLIES/ SERVICES | 15C. QUANTITY | 15D. UNIT | 15E. UNIT PRICE | 15F. AMOUNT |
|---|---|---|---|---|---|
| | **SEE SCHEDULE** | | | | |
| | **15G. TOTAL AMOUNT OF CONTRACT** | | | | **$2,440,796.00** |

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| (X) | SEC. | DESCRIPTION | PAGE(S) | (X) | SEC. | DESCRIPTION | PAGE(S) |
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| | | **PART I - THE SCHEDULE** | | | | **PART II - CONTRACT CLAUSES** | |
| X | A | SOLICITATION/ CONTRACT FORM | 1 | | I | CONTRACT CLAUSES | |
| | B | SUPPLIES OR SERVICES AND PRICES/ COSTS | | | | **PART III – LIST OF DOCUMENTS, EXHIBITS AND OTHER ATTACH.** | |
| | C | DESCRIPTION/ SPECS./ WORK STATEMENT | | | J | LIST OF ATTACHMENTS | |
| | D | PACKAGING AND MARKING | | | | **PART IV - REPRESENTATIONS AND INSTRUCTIONS** | |
| | E | INSPECTION AND ACCEPTANCE | | | K | REPRESENTATIONS, CERTIFICATIONS AND OTHER STATEMENTS OF OFFERORS | |
| | F | DELIVERIES OR PERFORMANCE | | | | | |
| | G | CONTRACT ADMINISTRATION DATA | | | L | INSTRS., CONDS., AND NOTICES TO OFFERORS | |
| | H | SPECIAL CONTRACT REQUIREMENTS | | | M | EVALUATION FACTORS FOR AWARD | |

CONTRACTING OFFICER WILL COMPLETE ITEM 17 (SEALED-BID OR NEGOTIATED PROCUREMENT) OR 18 (SEALED-BID PROCUREMENT) AS APPLICABLE

17. [ ] CONTRACTOR'S NEGOTIATED AGREEMENT Contractor is required to sign this document and return copies to issuing office.) Contractor agrees to furnish and deliver all items or perform all the services set forth or otherwise identified above and on any continuation sheets for the consideration stated herein. The rights and obligations of the parties to this contract shall be subject to and governed by the following documents: (a) this award/contract, (b) the solicitation, if any, and (c) such provisions, representations, certifications, and specifications, as are attached or incorporated by reference herein. (Attachments are listed herein.)

18. [ X ] SEALED-BID AWARD (Contractor is not required to sign this document.)
Your bid on Solicitation Number _____
REF: See 00800 Award Specific T & C
including the additions or changes made by you which additions or changes are set forth in full above, is hereby accepted as to the terms listed above and on any continuation sheets. This award consummates the contract which consists of the following documents: (a) the Government's solicitation and your bid, and (b) this award/contract. No further contractual document is necessary. (Block 18 should be checked only when awarding a sealed-bid contract.)

| 19A. NAME AND TITLE OF SIGNER (Type or print) | 20A. NAME OF CONTRACTING OFFICER |
|---|---|
| | TERESA PARKER-REESER / GRANTS OFFICER<br>TEL: 301-619-2171 EMAIL: Teresa.M.ParkerReeser.civ@mail.mil |

| 19B. NAME OF CONTRACTOR | 19C. DATE SIGNED | 20B. UNITED STATES OF AMERICA | 20C. DATE SIGNED |
|---|---|---|---|
| BY _____<br>(Signature of person authorized to sign) | | BY _____<br>(Signature of Contracting Officer) | 24-Sep-2017 |

Section 00010 - Solicitation Contract Form

| ITEM NO | SUPPLIES/SERVICES | QUANTITY | UNIT | UNIT PRICE | AMOUNT |
|---|---|---|---|---|---|
| 0001 | | | | | $2,440,796.00 |
| | Grant - OR160026<br>COST<br>Peer Reviewed Orthopedic Research Program<br>Clinical Translational Research Award<br><br>FOB: Destination | | | | |
| | | | | ESTIMATED COST | $2,440,796.00 |

| ITEM NO | SUPPLIES/SERVICES | QUANTITY | UNIT | UNIT PRICE | AMOUNT |
|---|---|---|---|---|---|
| 000101 | | | | | $0.00 |
| | FY16 OR160026 Funding<br>COST<br>Peer Reviewed Orthopedic Research Program<br>Clinical Translational Research Award<br>FOB: Destination<br>PURCHASE REQUEST NUMBER: 0011096131 | | | | |
| | | | | ESTIMATED COST | $0.00 |
| | ACRN AA<br>CIN: GFEBS001109613100001 | | | | $1,459,924.16 |

| ITEM NO | SUPPLIES/SERVICES | QUANTITY | UNIT | UNIT PRICE | AMOUNT |
|---|---|---|---|---|---|
| 000102 | | | | | $0.00 |
| | FY17 OR160026 Funding<br>COST<br>Peer Reviewed Orthopedic Research Program<br>Clinical Translational Research Award<br>FOB: Destination<br>PURCHASE REQUEST NUMBER: 0011096131 | | | | |
| | | | | ESTIMATED COST | $0.00 |
| | ACRN AB<br>CIN: GFEBS001109613100002 | | | | $980,871.84 |

## DELIVERY INFORMATION

| CLIN | DELIVERY DATE | QUANTITY | SHIP TO ADDRESS | DODAAC |
|---|---|---|---|---|
| 0001 | POP 30-SEP-2017 TO 29-SEP-2021 | N/A | FORT DETRICK - CDMRP<br>FORT DETRICK - CDMRP<br>1120 FORT DETRICK<br>FREDERICK MD 21702<br>FOB: Destination | W91ZSQ |
| 000101 | POP 30-SEP-2017 TO 29-SEP-2021 | N/A | N/A<br>FOB: Destination | |
| 000102 | POP 30-SEP-2017 TO 29-SEP-2021 | N/A | N/A<br>FOB: Destination | |

## ACCOUNTING AND APPROPRIATION DATA

AA: 097201620170130000183103333337410 R.0002688.6.1 6100.9000021001
COST CODE: A7444
AMOUNT: $1,459,924.16
CIN GFEBS001109613100001: $1,459,924.16

AB: 097201720180130000183103333337410 R.0002688.7.1 6100.9000021001
COST CODE: A7444
AMOUNT: $980,871.84
CIN GFEBS001109613100002: $980,871.84

CLAUSES INCORPORATED BY FULL TEXT

**U.S. ARMY MEDICAL RESEARCH ACQUISITION ACTIVITY**
**AWARD SPECIFIC RESEARCH TERMS AND CONDITIONS**
**WITH INSTITUTIONS OF HIGHER EDUCATION, HOSPITALS, AND NON-PROFIT ORGANIZATIONS**

**DIVISION I – AWARD COVER PAGES**

**Principal Investigator** Dr. Kevin Hildebrand

**Project Title** Prevention of Post-Traumatic Contractures with Ketotifen II (PERK II)

**Technical Abstract**

**Background:**
This proposal pertains to the FY16 PRORP CTA Focus Area on Surgical Care – Extremity Fractures. This research optimizes patient outcomes through prevention of post-traumatic joint contractures following fractures. Post-traumatic joint contractures, or loss of motion after injury, are a debilitating condition following elbow trauma. Limited elbow motion interferes with feeding, dressing, grooming, and reaching for objects, which markedly reduces the quality of life. Many affected individuals are in the 20 – 60 year age group and thus elbow contractures limit productivity in civilian and military populations. Our laboratory research on post-traumatic joint contractures over the last 18 years has implicated a myofibroblast-mast cell-neuropeptide axis of fibrosis in the joint capsule, the critical structure limiting joint motion. We have demonstrated in a rabbit model of posttraumatic contractures that ketotifen, a mast cell stabilizer that prevents growth factor release, decreased contracture severity by 50% concomitant with decreased numbers of myofibroblasts, mast cells, neuropeptide containing nerve fibres, and measures of fibrosis in the joint capsule. These results are very exciting because ketotifen is the first and only agent demonstrated to significantly decrease contracture severity that also has a wide safety profile, has been used in the chronic treatment of asthma for over 40 years in humans, is available as an oral preparation, and is low cost. Recent advances have positioned us to apply for the FY16 PRORP CTA. These include experiments revealing a dose-response effect of ketotifen for joint contracture severity inhibition in the preclinical model of post-traumatic contractures, completion of the recruitment phase for an randomized clinical trial (RCT) comparing one dose of ketotifen (5 mg twice daily) administered over 6 weeks to a lactose placebo for the prevention of post-traumatic elbow contractures (ClinicalTrials.gov Identifier NCT01902017), and the implementation of a CTDA from the FY14 PRORP funding cycle (eBRAP Log No OR140142) with the purpose to develop the infrastructure to conduct a multicenter Phase III randomized, double-blind, placebocontrolled

clinical trial to compare multiple doses of ketotifen to a lactose placebo. These three advances highlight the clinical trial expertise in Calgary, the need to consider a dosing effect for ketotifen, and the establishment of the infrastructure for a multicenter clinical trial.
**Research Hypothesis:** Ketotifen is superior to a lactose placebo in reducing joint contracture severity in adult participants with isolated elbow fractures or dislocations.
**Primary Objective**: To determine if ketotifen given within 7 days of injury can reduce post-traumatic elbow joint contractures when compared to placebo.
**Secondary Objectives**: 1) To ascertain the optimal dose of ketotifen and 2) to compare adverse events in ketotifen and placebo groups.
**Trial Design:** A Phase III randomized, controlled, double blinded multicenter trial with 3 parallel groups (ketotifen 2 mg or 5 mg or lactose placebo twice daily for 6 weeks) and a primary endpoint of elbow extensionflexion range of motion (ROM) arc at 12 weeks post-randomization. Eligibility: age ≥ 18 years old; isolated distal humerus and/or proximal ulna and/or proximal radius fractures and/or elbow dislocations requiring an operation; injury ≤ 7 days; able to mobilize elbow within 2 weeks of injury, no previous elbow contracture or arthritis. Outcome Measures: ROM; Disability Arm, Shoulder, Hand; Oxford Elbow Score; radiographs; reoperation 2 – 52 weeks post-randomization.
**Military Benefit and Clinical Impact:**
A recent review of extremity injuries in war by the US military has highlighted joint stiffness and contractures as a major complication that limits function. Injuries to Service members also occur in training exercises. Ketotifen has a long history of human clinical use with an oral route of administration, wide safety profile, and low cost. It is the only pharmaceutical possibility available in the foreseeable future. Easy transportability of ketotifen has military relevance. Service members can be returned to full-duty status either sooner than is typical, or Service members and Veteranss can enjoy a higher quality of life, following elbow injuries. A related potential use for ketotifen is after surgical release of post-traumatic elbow contractures to enhance the improvement in motion after the procedure. Joint contractures complicate other extremity injuries and the results of this trial would be relevant in these cases. Another procedure where contractures are a postoperative complication is total knee arthroplasty, which is commonly performed in civilian and Veterans populations. Adjuncts to operative reversal of contractures following knee replacements could be an indication for ketotifen. In addition to developing a translational, scientifically sound therapy for joint fibrosis and contracture through repurposing an established drug for a new indication, our findings might stimulate research in other conditions characterized by fibrosis that affects the lung, kidney, heart, liver, and skin.

**Recipient's Business Official**

Authorized Official: Dallas Callaway
Title: Research Grants Officer
Phone: 403-210-9815
Email: dacallaw@ucalgary.ca
DUNS Number: 207663915

**Grants Administration Office**

Grants Specialist: Kenneth Grenier
Phone: 301-619-2728
Email: kenneth.e.grenier2.civ@mail.mil

**Grants Officer's Representative**

Congressionally Directed Medical Research Program Office
Phone: 301-619-7071
Email: usarmy.detrick.medcom-cdmrp.mbx.cdmrp-reporting@mail.mil

**Applicability**

These award specific research terms and conditions are applicable to assistance agreement awards (grants and cooperative agreements) issued by the US Army Medical Research Acquisition Activity (USAMRAA) made with institutions of higher education, hospitals, and other non-profit organizations.

**Authorities**

This new award is a grant made under the authority of 10 U.S.C. 2358.

This award is governed by the guidance in 2 Code of Federal Regulations (CFR) part 200, "Uniform Administrative Requirements, Cost Principles, and Audit Requirements for Federal Awards," as modified and supplemented by the Department of Defense's (DoD) interim implementation found at 2 CFR part 1103, "Interim Grants and Cooperative Agreements Implementation of Guidance in 2 CFR part 200" (79 FR 76047, December 19, 2014), all of which are incorporated herein by reference.*

Provisions of Chapter I, Subchapter C of Title 32, CFR, "DoD Grant and Agreement Regulations," parts 26, 28, 34, 37, and 1125 continue to be in effect and are incorporated herein by reference, with applicability as stated in those provisions.

For nonprofit organizations identified in Appendix VIII to 2 CFR part 200, "Nonprofit Organizations Exempted From Subpart E – Cost Principles," and for subawards to commercial organizations, the cost principles in part 31 of Chapter 1 of Title 48, CFR, "Federal Acquisition Regulation" (FAR), and part 231 of Chapter 2 of Title 48, "DoD FAR Supplement," are incorporated herein by reference, with applicability as stated in those provisions.

*Note that OMB amended 2 CFR 200.110(a) on September 10, 2015, to permit recipients to continue to comply with the procurement standards in previously applicable OMB guidance, rather than the procurement standards in 2 CFR 200.317-200.326, through the end of the two recipient fiscal years that begin on or after December 26, 2014. DoD implemented those previous procurement standards in DoDGARs part 32 (32 CFR part 32) for institutions of higher education, hospitals and other nonprofit organizations and in DoDGARs part 33 (32 CFR part 33) for States and local and Indian tribal governments. If you choose to use those previous procurement standards, rather than the standards in PROC Articles I and II of the DoD R&D General T&Cs, you must document that decision in your internal procurement policies.

Copies of the above can be obtained from:

Office of Management and Budget
EOP Publications Office
New Executive Office Building
725 17th Street, NW, Room 2200
Washington, DC 20503
Telephone: (202) 395-7332
Website: http://www.whitehouse.gov/omb/

**Terms and Conditions Incorporated by Reference**

The following terms and conditions are incorporated herein by reference:

a. Division III - USAMRAA General Research Terms and Conditions with Institutions of Higher Education, Hospitals, and Non-Profit Organizations (effective February 2017), available at http://www.usamraa.army.mil/index.cfm?ID=12&Type=3.

b. The DoD R&D General Terms and Conditions (July 2016), available at http://www.onr.navy.mil/Contracts-Grants/submit-proposal/grants-proposal/grants-terms-conditions.aspx.

These USAMRAA Award Specific Research Terms and Conditions are in addition to the terms and conditions incorporated above.

**Order of Precedence**

Any inconsistencies in the requirements of this award will be resolved in the following order:

a. Federal statutes
b. Federal regulations
c. 2 CFR part 200 with amendments, as modified and supplemented by DoD's interim implementation found in 2 CFR part 1103
d. Division II - USAMRAA Award Specific Research Terms and Conditions
e. Division III - USAMRAA General Research Terms and Conditions with Institutions of Higher Education, Hospitals, and Non-Profit Organizations (effective February 2017)
f. DoD R&D General Terms and Conditions (July 2016)

**Acceptance of Award**

You are not required to countersign this award. In case of disagreement with any requirements in this award, contact the USAMRAA Grants Officer in order to resolve the issue(s). Do not assess any costs to the award or accept any payments until the issue(s) is resolved. Note, however, that initiating performance under this award constitutes acceptance of this award, including the terms and conditions.

**Catalog of Federal Domestic Assistance Number:** 12.420 - Military Medical Research and Development

**Statement of Work and Budget**

The revised Statement of Work (SOW) date 31 July 2017 and the revised budget dated 18 September 2017 for your application submitted in response to the Fiscal Year 2016 DoD Peer Reviewed Orthopedic Research Program Announcement (Funding Opportunity Announcement Number W81XWH-16-PRORP-CTA, which closed 7 December 2016) are incorporated herein by reference.

**Recipient's Indirect Cost Rate at the Start of the Performance Period:** 39.8%

**Funding Overview**

| | Federal funds | Cost Sharing | Total amount |
|---|---|---|---|
| Obligated or deobligated this action | $2,440,796 | N/A | $2,440,796 |
| Cumulative obligations to date, including this and previous actions | $2,440,796 | N/A | $2,440,796 |
| Planned project costs in the currently approved budget through the end of the period of performance, to include any future incremental funding obligations | $2,440,796 | N/A | $2,440,796 |
| Total value, which includes any unexercised options for which amounts were established in the award | $2,440,796 | N/A | $2,440,796 |

**DIVISION II – AWARD SPECIFIC RESEARCH TERMS AND CONDITIONS**

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**AWARD SPECIFIC TERMS AND CONDITIONS**

**1. Award Type**

This is a cost-type award in support of basic or applied research. Construction activities under this award are not authorized. (Reference Department of the Army Pamphlet 420-11, dated 18 March 2010, for additional information regarding construction activities.)

***2.* Award Modification**

The only method by which the award may be modified is by a formal, written modification signed by the USAMRAA Grants Officer. No other communications, whether oral or in writing, are valid to change the terms and conditions of this award.

**3. Maximum Obligation**

The maximum obligation of the Federal Government for support of this award will not exceed the award amount specified in the award cover pages, as modified. This award will not be modified to provide additional funds for such purposes as reimbursement for unrecovered indirect costs resulting from the establishment of final negotiated rates or for increases in salaries, fringe benefits, changes in exchange rates, or other costs. You may rebudget allowable costs in accordance with applicable cost principles and in accordance with the prior approval requirements as stated in this award.

**4. Expiration of Funds**

(a) Funds obligated on this award are available for use for a limited period based on the fiscal year (FY) of the funds. That time is considered when establishing your period of performance. **This award is funded with FY 2016 funds which will expire for use on September 30, 2022 and FY 2017 funds which will expire for use on September 30, 2023.** If the final budget period of this award has expiring funds and you do not anticipate expending the total amount by the end of the period of performance, six months before the end of the period of performance contact the Grants Specialist identified in the cover pages of this award**.**

(b) It is extremely important that you monitor the established milestones, timelines, expenditures and invoicing to make sure the project is on schedule and that you voucher promptly. **If this award has funds that will expire on September 30, 2022, submit the final SF270 at least 30 days before September 30, 2022 in order to allow sufficient time to process and pay the voucher. If this award has funds that will expire on September 30, 2023, submit the final SF270 at least 30 days before September 30, 2023 in order to allow sufficient time to**

**process and pay the voucher.** If you have not submitted a final SF270 and been paid before the expiration date of these funds, any excess funds will be deobligated from the award at that time.

**5. Fixed-Amount Awards and Fixed-Amount Subawards**

You are not authorized to treat this award or any subawards that you enter into under this award, at any tier, as fixed-amount awards. The inherently unpredictable nature of basic and applied research makes it rarely, if ever, possible to define specific research outcomes in advance, which makes fixed-amount awards inappropriate for research. This is not applicable to procurement contracts entered into under this award for acquisition of supplies, equipment, or general support services you need to carry out the project or program.

**6. Prior Approval Requirements**

You must request prior approval from the USAMRAA Grants Officer for any of the following program or budget revisions:

a. A change in the scope or objective of the project or program under the award, even if there is no associated budget revision that requires our prior approval.

b. A change in a key person(s) identified in the cover pages of the award.

c. The approved principal investigator's (PI) or project director's disengagement from the project for more than three months, or a 25 percent reduction in his or her time devoted to the project.

d. The inclusion of direct costs that require prior approval in accordance with the applicable cost principles, as identified in FMS Article III of the DoD R&D General Terms and Conditions (July 2016). Note the following requirements and limits:

(1) In accordance with applicable cost principles, you must request prior written approval for the incurrence of special or unusual costs.

(2) The requirement for prior written approval of capital expenditures for equipment that is to be used primarily in carrying out the project or program supported by the award is waived for equipment with a unit cost of $25,000 or less. Capital expenditures for equipment with a unit cost over $25,000 require the USAMRAA Grants Officer's prior approval. **Note that equipment acquired under the award and charged as direct project costs must be necessary for the conduct of the research project supported by the award. You are prohibited from acquiring equipment under the award merely for the purpose of using unobligated balances.**

e. A subaward to another entity under which it will perform a portion of the substantive project or program under the award if it was not included in the approved budget. This does not apply to your contracts for acquisition of supplies, equipment, or general support services you need to carry out the project or program.

f. The transfer (relocation) of the PI and/or research project to another entity.

g. Reimbursing a DoD Military Treatment Facility (MTF) for costs incurred if the MTF is involved in the award. Reimbursing these costs is generally prohibited and only approved under unusual and extraordinary circumstances.

h. Any change in the cost sharing or matching you provide under the award that is included in the approved budget.

i. The need arises for additional Federal funds to complete the project or program.

**7. Title to Property**

Property acquired in whole or in part with award funds is considered to be excepted property. As such, title is vested to you without further obligation to the Federal Government. Reference PROP Article IV of the DoD R&D General Terms and Conditions (July 2016).

**8. Financial Reporting Requirements**

a. You must submit Standard Form (SF) 425, "Federal Financial Report," for reporting on this award. Annual and final reports are required.

b. The Federal Financial Reporting period end dates fall on the end of the calendar year for annual reports (12/31), and the end date of the term of award for the final report. Submit annual reports no later than 90 days after the end of the calendar year. Submit final reports no later than 120 days after the end of the period of performance.

c. Submission Instructions:

(1) All SF425 reports must be submitted electronically through the web site https://www.usamraa.army.mil/pages/sf425. The form and instructions can be obtained on this site.

(2) Do not report multiple awards on one report. Each award must be reported separately on its own SF425.

(3) Do not combine multiple SF425s into one submission. Each form must be saved as a separate PDF and submitted individually.

**9. Patents and Inventions Reporting Requirements**

a. iEdison and annual reporting. You must electronically file Invention Disclosures and Patent Applications using the Interagency Edison (iEdison) system through the National Institutes of Health (https://s-edison.info.nih.gov/iEdison) within the times specified for reporting. In addition, you must report annually any inventions made during the year (within 30 days of the anniversary date of the award) on a DD Form 882, "Report of Inventions and Subcontracts." If there are no inventions during the year, no annual DD Form 882 is required. The DD Form 882 can be accessed at https://www.usamraa.army.mil.

b. Closeout report. A final DD Form 882 is required, whether or not you are reporting an invention. Submit the report within 120 days of end of the period of performance. List all inventions made during the period of performance or state "none," as applicable. The award will not be closed until you have met all reporting requirements.

c. Submit all DD882 reports electronically to usarmy.detrick.medcom-usamraa.mbx.aa4@mail.mil.

**10. Technical Reporting Requirements**

The following technical progress reports are required under this award:

**Quarterly Technical Reports**

a. For each year of the award, the PI must submit Quarterly Technical Progress Reports covering research results (positive and negative data) over a three month period (quarter). A reporting quarter begins with the start date of the award and restarts annually from that date for the entire period of performance. A Quarterly Technical Progress Report for the fourth quarter each year is not required, as the Annual Technical Report must incorporate all four quarters of progress.

b. Quarterly reports are the most immediate and direct contact between the PI and the Grants Officer's Representative (GOR). The reports provide the means for keeping the US Army Medical Research and Materiel

Command (USAMRMC) advised of developments and problems as the research effort proceeds. The reports also provide a measure against which funding decisions are made.

c. Prepare all Quarterly reports in accordance with the Quarterly Technical Progress Report format, available at http://www.usamraa.army.mil/index.cfm?ID=12&Type=3. Each item of the report format must be completed.

d. Each report must be submitted electronically, within 15 days after the end of each quarter, to the Grants Specialist and the GOR at the e-mail addresses specified in the front pages of this award. Name your file with your award number, followed by Year X Quarter Y Report (example: W81XWH-17-1-0665 Year 1 Quarter 1 Report.) If you have questions, contact the GOR.

e. Special Reports

Quad Charts: The Quad Chart (available on https://www.usamraa.army.mil) must be updated and submitted as an appendix.

**Annual/Final Technical Reporting Requirements**

a. Annual Reports

(1) Annual reports are required and must be prepared in accordance with the Research Performance Progress Report (RPPR). The RPPR is the uniform format for reporting performance progress on Federally-funded research projects and research-related activities.

(2) Annual reports must provide a complete summary of the research results (positive or negative) to date in direct alignment to the approved Statement of Work (SOW). The importance of the report to decisions relating to continued support of the research cannot be over-emphasized. An annual report must be submitted within 30 calendar days of the anniversary date of the award for the preceding 12 month period. If the award period of performance is extended by the USAMRAA Grants Officer, then an annual report must still be submitted within 30 days of the anniversary date of the award. A final report that describes the entire research effort is due upon completion of the extended performance date.

b. Final Reports. A final report must also be prepared in accordance with the RPPR and must be submitted within 120 calendar days of the end of the period of performance. The report must summarize the entire research effort, citing data in the annual reports and appended publications.

c. Prepare the annual and final reports in accordance with the RPPR format, available at http://www.usamraa.army.mil/index.cfm?ID=12&Type=3. Although there is no page limitation for the reports, each report must be of sufficient length to provide a thorough description of the accomplishments with respect to the approved SOW.

d. Reports, in electronic format (PDF or Word file only), must be submitted to https://ers.amedd.army.mil.

Additional information is available on the Researcher Resources website, available at https://mrmc.amedd.army.mil/index.cfm?pageid=researcher_resources.technical_reporting

e. Special Reports

Quad Charts: The Quad Chart (available on https://www.usamraa.army.mil) must be updated and submitted as an appendix.

**11. Publication, Acknowledgement, and Public Release**

a. Publication. You are encouraged to publish results of the research, unless classified, in appropriate media. Submit one copy of each paper to the GOR simultaneously with its submission for publication. Forward copies of

all publications resulting from the research to the USAMRAA Grants Officer or Grants Specialist as they become available, even though publication may in fact occur subsequent to the termination date of the award. (See Section C of the DoD R&D General Terms and Conditions for the charging of publication costs incurred after the period of performance.)

b. Acknowledgment. You agree that in the release of information relating to this award such release will include the statements below, as applicable. "Information" includes, but is not limited to, news releases, articles, manuscripts, brochures, advertisements, still and motion pictures, speeches, trade association meetings, and symposia.

(1) "The U.S. Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick MD 21702-5014 is the awarding and administering acquisition office" and;

(2) "This work was supported by the Office of the Assistant Secretary of Defense for Health Affairs, through the Peer Reviewed Orthopedic Research Program under Award No. W81XWH-17-1-0665. Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the Department of Defense."

(3) "In conducting research using animals, the investigator(s) adheres to the laws of the United States and regulations of the Department of Agriculture."

(4) "In the conduct of research utilizing recombinant DNA, the investigator adhered to NIH Guidelines for research involving recombinant DNA molecules."

(5) "In the conduct of research involving hazardous organisms or toxins, the investigator adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories."

c. Public release. Prior to release to the public, you must notify the USAMRAA Grants Officer and the GOR of the following: planned news releases, planned publicity, advertising material concerning project work, and planned presentations to scientific meetings. This provision is not intended to restrict dissemination of research information; the purpose is to inform the USAMRMC of planned public release of information on USAMRMC-funded research in order to adequately respond to inquiries and to be alert to the possibility of inadvertent release of information which could be taken out of context.

Failure to include the above statements and adhere to the above regulations, when required, may result in loss of funding and/or termination of this award.

**12. Payment Requests**

**Request for Payments - Fully Funded Award**

a. Payments. Payments will be made to you upon receipt of a "grant voucher" (used for both grants and cooperative agreements) submitted through the Wide Area Work Flow (WAWF) e-Business Suite in accordance with the Contract Line Item Number (CLIN) structure set forth in this award.

b. Payment requests can be either advance or reimbursement. Select "advance" or "reimbursement" on the grant voucher in WAWF.

c. In order to conserve administrative resources for both parties, you are encouraged to voucher no more frequently than monthly. **Failure to voucher at least quarterly may raise concerns about research progress and the need for continued funding.**

d. For any advance payment request, you should (1) submit the request approximately 10 days before you anticipate disbursing the requested amount for program purposes, and (2) you must provide an explanation regarding the need for the advance. Include your explanation in the "initiator" block under "comments" or attach an

explanation under "attachments." Advance payments must be limited to the minimum amount needed to meet your actual, immediate cash requirements for carrying out the purpose of the approved program or project, including direct program or project costs and a proportionate share of any allowable indirect costs. All advances must be approved by the Grants Officer. Grants Officer approval will be through approval of the grant voucher.

e. All payments will be made by Electronic Funds Transfer (EFT) to your institution's financial account listed in the System for Award Management (SAM) (available at https://www.sam.gov ). Failure to update SAM ensuring active account status will result in nonpayment.

f. Failure to submit required Technical Reports or Federal Financial Reports (SF425s) may delay payments or result in nonpayment.

g. If you fail to perform, the grant voucher will be rejected.

h. Interest Bearing Account. You must deposit all advance payments into an interest bearing account unless one of the following applies:

1. You are exempted by applicable Treasury-State agreements in accordance with the Cash Management Improvement Act (31 USC 3335).
2. You receive less than $120,000 in Federal awards per year.
3. The best reasonably available interest bearing account would not be expected to earn interest in excess of $500 per year on Federal cash balances.
4. The depository would require an average or minimum balance so high that it would not be feasible within the expected Federal and non-Federal cash resources.

i. Interest over the amount of $500 per year must be remitted annually to the U.S. Department of Health and Human Services, Payment Management System, P.O. Box 6021, Rockville, Maryland 20852. A copy of the transmittal letter stating the amount of interest remitted must be sent electronically to usarmy.detrick.medcom-usamraa.mbx.aa4@mail.mil.

**NOTE: This award is comprised of a clinical study or trial that requires Human Use approval from the USAMRMC Office of Research Protection (ORP). Grant vouchers may be submitted for payments for the first 12 months of this award. No grant voucher may be submitted thereafter until you provide a copy of the ORP approval notification to the cognizant Grants Specialist at** usarmy.detrick.medcom-usamraa.mbx.aa4@mail.mil**.**

**13. Electronic Payment Instructions**

a. The Wide Area Work Flow (WAWF) e-Business Suite is the required method to electronically process your requests for payments. Once on the WAWF e-Business Suite web site, select the Invoicing, Receipt, Acceptance, and Property Transfer (iRAPT) button to electronically submit "grant vouchers" (used for both grants and cooperative agreements). You must (i) register to use WAWF at https://wawf.eb.mil and (ii) ensure an electronic business point of contact (POC) is designated in the System for Award Management (SAM) site at https://www.sam.gov within ten (10) calendar days prior to requesting a payment for this award.

b. Questions concerning specific payments should be directed to the Defense Finance and Accounting Service (DFAS), Indianapolis, at 1-888-332-7366. **You can also access payment and receipt information using the "myInvoice" button in WAWF at** https://wawf.eb.mil. The award number or grant voucher number will be required to inquire about the status of the payment.

c. The following codes and information are required to initiate the grant voucher and assure successful flow of WAWF documents.

TYPE OF DOCUMENT: **Grant Voucher** ***(Used for both grants and cooperative agreements)***

CAGE CODE: **1C344**

ISSUE BY DODAAC: **W81XWH**

ADMIN BY DODAAC: **W81XWH**

INSPECT BY DODAAC: **W81XWH**

ACCEPT BY DODAAC: **W81XWH**

SHIP TO DODAAC: **W81XWH**

LOCAL PROCESSING OFFICE DODDAC: **Not Applicable**

PAYMENT OFFICE FISCAL STATION CODE**: HQ0490**

EMAIL POINTS OF CONTACT LISTING:
INSPECTOR: **usarmy.detrick.medcom-usamraa.mbx.aa4@mail.mil**
ACCEPTOR**: usarmy.detrick.medcom-usamraa.mbx.aa4@mail.mil**
RECEIVING OFFICE POC: **usarmy.detrick.medcom-usamraa.mbx.aa4@mail.mil**
GRANT ADMINISTRATOR: **Leave Blank**
GRANTS OFFICER: **Leave Blank**
ADDITIONAL CONTACT: **usarmy.detrick.medcom-usamraa.mbx.aa4@mail.mil**

***14.*** **Closeout Requirements**

a. In order to close this award, you must submit the following documents within 120 calendar days of the end of the period of performance:

(1) Final SF425, "Federal Financial Report." Submit to: https://www.usamraa.army.mil/pages/sf425. Form and instructions are available on the web site.

(2) Final Technical Report. Submit to: https://ers.amedd.army.mil. Forms and instructions are available on the web site.

(3) Final DD Form 882, "Report of Inventions and Subcontracts." Submit to: usarmy.detrick.medcom-usamraa.mbx.aa4@mail.mil. Form is available on web site https://www.usamraa.army.mil).

(4) Property Acquired with Award Funds, if applicable. [Reference PROP Article IV of the DoD R&D General Terms and Conditions (July 2016).]

(a) If title to property (equipment and supplies) is excepted property, there is no further obligation to the Federal Government.

(b) If title to equipment under this award is non-excepted property, you must provide a cumulative listing of nonexpendable personal property acquired with award funds. Submit this on your organization's letterhead. Submit to: usarmy.detrick.medcom-usamraa.mbx.aa4@mail.mil.

(c) If title to supplies under this award is non-excepted property, you must submit a statement that: (i) there is, or is not, a residual inventory of unused supplies exceeding $5,000 in total aggregate value; and (ii) if there is, state whether or not the unused items will be needed on other Federally sponsored projects or programs. Submit this on your organization's letterhead. Submit to usarmy.detrick.medcom-usamraa.mbx.aa4@mail.mil.

b. In the event a final audit has not been performed prior to the closing of this award, the Federal Government retains the right to recover an appropriate amount after fully considering the recommendations on disallowed costs resulting from the final audit.

c. You must promptly refund any unspent balances of funds the DoD Component has advanced or paid that is not authorized to be retained by you. Make check payable to the U.S. Treasury and mail to:

USAMRAA
Attn: MCMR-AAP-C
Federal Award Identification No. W81XWH-17-1-0665
820 Chandler Street
Fort Detrick, Maryland 21702-5014

**15. Prohibition of Use of Laboratory Animals**

Notwithstanding any other terms and conditions contained in this award or incorporated by reference herein, the recipient is expressly forbidden to use or subcontract for the use of laboratory animals in any manner whatsoever without the express written approval of the USAMRMC, Animal Care and Use Review Office (ACURO). Written authorization to begin research under applicable protocol(s) proposed for this award will be issued in the form of an approval letter from the USAMRMC ACURO to the recipient with a copy to the USAMRAA Grants Officer. Furthermore, modifications to already approved protocols require approval by ACURO prior to implementation. For each fiscal year, the recipient must maintain, and upon request from ACURO, submit animal usage information.

Noncompliance with any of these terms and conditions may result in withholding of funds and/or the termination of the award.

The Animal Care and Use Office requirements can be accessed at https://mrmc.amedd.army.mil/index.cfm?pageid=research_protections.acuro.

**16. Prohibition of Use of Human Subjects**

Research under this award involving the use of human subjects, to include research involving the secondary use of human biospecimens and/or human data, cannot begin until the USAMRMC's Office of Research Protections (ORP) provides authorization that the research may proceed. The USAMRMC ORP will issue written approval to begin research under separate notification to you. Written approval to proceed from the USAMRMC ORP is also required for any subrecipient that will use funds from this award to conduct research involving human subjects.

The USAMRMC ORP conducts site visits as part of its responsibility for compliance oversight. Accurate and complete study records must be maintained and made available to representatives of the USAMRMC as a part of their responsibility to protect human subjects in research. Research records must be stored in a confidential manner so as to protect the confidentiality of subject information.

The recipient is required to adhere to the following reporting requirements:

Submission of substantive modifications to the protocol, continuing review documentation, and the final report as outlined in the USAMRMC ORP approval memorandum.

Unanticipated problems involving risks to subjects or others, subject deaths related to participation in the research, clinical holds (voluntary or involuntary), and suspension or termination of this research by the IRB, the institution, the Sponsor, or regulatory agencies, must be promptly reported to the USAMRMC ORP.

Change in subject status when a previously enrolled human subject becomes a prisoner must be promptly reported to the USAMRMC ORP HRPO.

The knowledge of any pending compliance inspection/visits by the FDA, ORP, or other government agency concerning this clinical investigation or research, the issuance of Inspection Reports, FDA Form 483, warning letters or actions taken by any Regulatory Agencies, and any instances of serious or continuing noncompliance with regulatory requirements that relate to this clinical investigation or research, must be reported immediately to the USAMRMC ORP.

Non-compliance with these terms and conditions may result in withholding of funds and/or the termination of the award.

DoD requirements for human subjects research, including 32 CFR Part 219, DoD Instruction 3216.02, and USAMRMC ORP Human Research Protection Office submission instructions can be accessed at https://mrmc.amedd.army.mil/index.cfm?pageid=research_protections.hrpo.

**17. Prohibition of Use of Human Cadavers**

Research, development, testing and evaluation (RDT&E), education or training activities involving human cadaveric specimens under this award shall not begin until approval is granted in accordance with the Army Policy for Use of Human Cadavers for RDT&E, Education, or Training, 20 April 2012 (https://mrmc.amedd.army.mil/index.cfm?pageid=research_protections.overview).

The USAMRMC Office of Research Protections (ORP) is the Action Office (usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil) for this policy. Approval must be obtained from the USAMRMC ORP. Award recipients must coordinate with the supporting/funding Army organization to ensure that proper approvals are obtained. ORP will issue written approvals to begin under separate notification to the recipient. Written approval to proceed from the USAMRMC ORP is also required for any subrecipient that will use funds from this award to conduct RDT&E, education or training involving human cadaveric specimens.

Recipients must promptly report problems related to the conduct of the activity involving cadavers or the procurement, inventory, use, storage, transfer, transportation, and disposition of cadavers to the USAMRMC ORP.

Recipients must maintain complete records of the activity.

The USAMRMC or designees must be permitted to observe the activity upon request and/or audit activity records to ensure compliance with the approved protocol or applicable regulatory requirements.

Non-compliance with these terms and conditions may result in withholding of funds and/or the termination of the award.

**18. Interim Progress Review**

In addition to quarterly, annual, and final technical progress reports, the PI shall prepare for and participate in at least one Interim Progress Review (IPR) for each year of the project's term of award. Generally, the IPR will last no longer than two days and require no more than two overnight stays. It most likely will be held in the Fort Detrick, Maryland area, but may occur elsewhere in the U.S. The invitation and format for the IPR will be provided by the GOR at least 90 days prior to the scheduled date.

**19. Clinical Trial Registry**

Certain clinical trials are required by U.S. law to be registered on the National Institutes of Health database entitled "ClinicalTrials.gov." For those trials required to be registered (see http://prsinfo.clinicaltrials.gov/, "Support Materials, including Data Element Definitions"), PIs must register clinical trials individually on http://www.clinicaltrials.gov. PIs must use a Secondary Protocol ID number designation of "CDMRP-OR160026". If several protocols exist under the same application, the Secondary Protocol ID number must be designated "CDMRP- OR160026-A, B, C, etc.". Clinical trials must be registered prior to enrollment of the first patient. Failure to do so may result in a civil monetary penalty and/or the withholding or recovery of award funds as per U.S. Public Law 110-85.

**20. Required Start Date for Proposed Clinical Trial**

The proposed clinical trial, a FDA-regulated study, is required to begin no later than 29 September 2018. Non-compliance with this term and condition may result in withholding of funds and/or the termination of the award.

IND 136411

**FULL CLINICAL HOLD**

Kevin A. Hildebrand, MD
c/o Dr. Michael Bosse
P.O. Box 32861
Charlotte, NC 28232

Dear Dr. Hildebrand:

Please refer to your Investigational New Drug Application (IND) submitted July 30, 2017, received August 1, 2017, under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ketotifen fumarate.

Nikolay Nikolov, MD, Clinical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products, notified you through the August 30, 2017 telephone conversation with Alexandra Garven, that the study you proposed is on clinical hold and may not be initiated. The following are the specific deficiencies and the information needed to resolve the deficiencies:

21 CFR 312.42(b)(2)(i): Insufficient information to assess risks to human subjects

There are no data characterizing the drug-related substances (i.e., degradant/impurity profile) of the drug product. There is no assurance that the drug product will be compliant with its specification at the time of use in the clinical study.

Chemistry, Manufacturing, and Controls (CMC) information needed to resolve deficiencies:

1. Provide data characterizing the impurity profile of the drug product that you plan to use in the clinical study. As we had indicated previously, you may need to have a contract laboratory obtain these data in support of your IND if they cannot be obtained from the manufacturer.

2. Provide confirmation that the drug product will be used within its manufacturer's expiration dating period, during the clinical study. As we had suggested earlier, you may provide a photocopy of this information from the manufacturer's packaging.

Until you have submitted the required information and we notify you that you may initiate the clinical study, you may not legally initiate or resume clinical studies under this IND.

Please identify your response to the clinical hold issues as a "**CLINICAL HOLD COMPLETE RESPONSE.**" An incomplete response will not start the review clock. Your complete response submission should reference, by date, any information previously submitted necessary to fully

respond to these clinical hold issues. To facilitate a response to your submission, submit this information in triplicate to the IND. In addition, send a copy of the cover letter to Linda Ebonine.

Following receipt of your complete response to these issues, we will notify you of our decision within 30 days.

In addition, we have the following recommendations and/or requests that are not clinical hold issues. Your responses to any non-hold issues should be addressed in a separate amendment to the IND.

**CLINICAL:**

1. Since the proposed dose of ketotifen 5mg twice per day is greater than the approved doses of the medication, and there is no definitive safety data in pregnancy regarding ketotifen, we recommend that the protocol specifies highly efficient contraception (generally two forms of contraception) for women and men of childbearing potential while on the study medication.

2. We note that you are referring to the IND opening study as a "Phase III" study. However, from regulatory perspective, this is viewed as a proof-of concept study. As currently designed, the proposed study is not likely to be sufficient to support a marketing application. Thus, if you intend to develop the product for marketing, we recommend that you request a separate meeting with the Agency.

3. The dosing regimen in the proposed study does not include up-titration, as recommended in the approved Teva Canada labeling to minimize the initial sedation with ketotifen. Thus, we recommend that in the protocol, you employ an initial up-titration or if this is not feasible, clearly describe the potential risk of excessive sedation in the informed consent document. Related to this, the informed consent should advise the study participants to abstain from alcohol while on the study medication since the medication may potentiate the effects of alcohol.

**NONCLINICAL**:

4. To support further clinical development and/or a marketing application, submit complete study reports for all nonclinical studies. Refer to ICH M3(R2) guidance (Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals) for studies needed to support a marketing application. Alternatively, submit a letter of reference to the approved NDA for Zaditor.

**CLINICAL PHARMACOLOGY:**

5. Ketotifen is metabolized in the liver and its clearance may likely be reduced in patients with impaired liver function. Therefore, we recommend that you amend the study protocol to exclude patients with severe hepatic impairment.

6. Since 60-70% of ketotifen dose is excreted in urine as metabolites, there is a possibility of accumulation of ketotifen's metabolites in patients with severely impaired renal function. Therefore, we recommend that you amend the study protocol to exclude patients with severe renal impairment.

Please cite the IND number listed above at the top of the first page of any communications concerning this application. Each submission to this IND must be provided in triplicate, an original and two copies. Please include three originals of all illustrations which do not reproduce well. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary, Allergy, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Linda Ebonine, Regulatory Project Manager, at (240) 402-4483.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, MD, PhD
Division Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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LINDA EBONINE
09/07/2017

LYDIA I GILBERT MCCLAIN
09/07/2017
Acting Division Director

9240 Santa Fe Springs Rd
Santa Fe Springs, California 90670-2618
Tel: 562-948-2225, Fax: 562-948-5850

# Invoice

| | |
|---|---|
| Invoice No. | **Pro-forma** |
| Revision | Original |
| Invoice Date | 9/21/2017 |
| Page | 1 of 1 |

**Invoice To**

University of Calgary
3645 Peter Loughheed Centre 3500 26 Ave NE
Calgary, AB
Canada
Accounts Payable / Alexandra Garven

**Requested By**

University of Calgary
3645 Peter Loughheed Centre 3500 26 Ave NE
Calgary, AB
Canada
Alexandra "Alex" Garven

Project Name: (Zaditen) Ketotifen Fumarate

| Customer No. | Payment Terms | P.O. No. | Exova Job No. | Order Date |
|---|---|---|---|---|
| UA05130 | Net 30 days | COD | 216346 | 09/15/2017 |

| Service Description | Price | Quantity | Total |
|---|---|---|---|
| Lactose Monohydrate (as Lactose) by HPLC-PAD | $600.00 | 1 | $600.00 |
| Magnesium Assay by SOP 7040, Rev 13 | $600.00 | 1 | $600.00 |
| Method Development for Ketotifen Fumarate Assay in Drug Product by HPLC-UV/Vis | $3,000.00 | 1 | $3,000.00 |
| QA Data Package | $750.00 | 1 | $750.00 |
| Residual Solvents by SOP 5220, Rev 6 | $500.00 | 1 | $500.00 |
| Selected Metals by SOP 7040, Rev 13 | $330.00 | 1 | $330.00 |
| Supplies | $1,000.00 | 1 | $1,000.00 |

**Remit To :**

Exova Inc.
Lockbox # 774214
4214 Solutions Center
Chicago, IL 60677-4002

**Wire Transfer:**

Exova Inc.
Account #4121487573
Wells Fargo Bank, N.A.
420 Montgomery Street
San Francisco, CA 94104
ABA-121000248
SWIFT-WFBIUS6S

| | |
|---|---|
| Subtotal | $6,780.00 |
| | |
| | $0.00 |
| **Total Payable in USD** | **$6,780.00** |

Find all about us at http://www.exova.com

Conjoint Health Research Ethics Board
Research Services Office
2500 University Drive, NW
Calgary AB T2N 1N4
Telephone: (403) 220-2297
chreb@ucalgary.ca

# CERTIFICATION OF INSTITUTIONAL ETHICS APPROVAL

The Conjoint Health Research Ethics Board (CHREB), University of Calgary has reviewed and approved the following research protocol:

| | |
|---|---|
| Ethics ID: | REB17-0609 |
| Principal Investigator: | Kevin Hildebrand |
| Co-Investigator(s): | Kevin Hildebrand<br>Jeremy LaMothe<br>Ian Le<br>Nicholas George H. Mohtadi |
| Student Co-Investigator(s): | There are no items to display |
| Study Title: | PrEvention of posttraumatic contractuRes with Ketotifen II (PERK II) |
| Sponsor: | United States of America Department of Defense |

**Effective:** September 11, 2017 **Expires:** September 11, 2018

This study has been reviewed by the full Conjoint Health Research Ethics Board of the University of Calgary on September 7, 2017.

**The following documents have been approved for use:**

- Consent Form, 1.0, August 18, 2017
- FINAL_OES_English_UK_Sample-1
- Disability of the Arm, Shoulder and Hand (DASH) Questionnaire
- Case Report Forms, 1.0, July 24, 2017
- PERK II Protocol V1.0 20170731, 1.0, July 31, 2017
- Investigator's Brochure
- Product Monograph, 3.0
- Safety Data Sheet

The CHREB is constituted and operates in accordance with the current version of the *Tri-Council Policy*

*Statement: Ethical Conduct for Research Involving Humans* (TCPS); International Conference on Harmonization E6: Good Clinical Practice Guidelines (ICH-GCP); Part C, Division 5 of the Food and Drug regulations, Part 4 of the Natural Health Product Regulations and the Medical Device Regulations of Health Canada; Alberta's Health Information Act, RSA 2000 cH-5; and US Federal Regulations 45 CFR part 46, 21 CFR part 50 and 56.

You and your co-investigators are not members of the CHREB and did not participate in review or voting on this study.

***Restrictions:***

**This Certification is subject to the following conditions:**

1. Approval is granted only for the research and purposes described in the application.
2. Any modification to the approved research must be submitted to the CHREB for approval.
3. An annual application for renewal of ethics certification must be submitted and approved by the above expiry date.
4. A closure request must be sent to the CHREB when the research is complete or terminated.

Approval by the REB does not necessarily constitute authorization to initiate the conduct of this research. The Principal Investigator is responsible for ensuring required approvals from other involved organizations (e.g., Alberta Health Services, community organizations, school boards) are obtained.

| **Approved By:** | **Date:** |
| --- | --- |
| Stacey A. Page, PhD, Chair , CHREB | September 11, 2017 |

*Note: This correspondence includes an electronic signature (validation and approval via an online system).*